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President

November 2, 1999

Food and Drug Administration
Dockets Management Branch (HFA-305)
5630 Fishers Lane
Room 1061
Rockville, Maryland 20852

Re: Draft Guidance for Industry on BA and BE Studies for Orally Administered Drug Products-General Considerations [Docket No. 99D-2729]

Dear Sir or Madam:

On behalf of the Science committee of the Generic Pharmaceutical Industry association (GPIA), I would like to submit comments to you on "Draft Guidance for Industry on BA and BE Studies for Orally Administered Drug Products-General Considerations", 64(171) FR, 48409, September 3, 1999.

GPIA is comprised of the manufacturers and distributors of generic medicines, as well as the providers of technical services and goods to these firms. Many of our members will be directly impacted by implementation of the subject draft guidance.

Thank you for the opportunity to submit our comments on the subject draft guidance. We would appreciate your consideration of these comments as you finalize the guidance.

Sincerely,

Alice E. Till, Ph.D.
President

CC E. Lane, Chair GPIA BA/BE Taskforce
V. Shah, FDA

99D-2729

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Comments from GPIA, November 1999

Guidance for Industry
BA and BE Studies for Orally Administered Drug Products — General Considerations
DRAFT GUIDANCE August 1999

I. INTRODUCTION.

Paragraph 3

Although some of the guidances recommend approaches that may result in small increases in regulatory burden (e.g., a recommendation for replicate study designs in this guidance (section III.A.4)), overall the general set of approaches delineated in the general core guidances results in a substantial reduction in regulatory burden.

Recommendation

If FDA finalizes this Guidance, it should include a recognition of the large increased in regulatory burden, and a justification of it.

Comment

The net effect of this Guidance is an increase in regulatory burden. This results from the wide application of the replicate design study recommended in this guidance. There is an emerging emphasis on the subject-by-formulation interaction as estimated according to the accompanying Guidance, "Average, population, and individual approaches to establishing BE". This is a new representation of the old argument that products shown to bioequivalent in healthy young men are not necessarily bioequivalent in patients. There have been many efforts to prove this argument and it has not been accomplished. The broad imposition of replicate design studies and the opinion that $\sigma_D \geq 0.15$ is reason for "concern" has no basis in scientific evidence. Two important elements of scientific evidence are rationality and repeatability. This change to establishing bioequivalence has met neither of these basic scientific criteria.

I. INTRODUCTION.

Paragraph 4

Once completed and finalized, these general core BA/BE guidances are designed to reduce the need for FDA drug-specific BA/BE guidances.

Recommendation

Keep this.

Comment

This is a good thing. The individual drug product guidances are frequently written or interpreted too narrowly.

II. BACKGROUND

B. Bioavailability

Paragraph 4, Sentence 4 to Paragraph 5, Sentence 1

Systemic exposure patterns reflect both release of the drug substance from the drug product and a series of possible presystemic actions on the drug substance after its release from the drug product.

Additional comparative studies should be performed to understand the relative contribution of these two separate processes to the systemic exposure pattern.

Recommendation

Exposure patterns reflect both release of the drug substance from the drug product and a series of possible post-absorption, presystemic and systemic actions on the drug substance after its release from the drug product.

Additional comparative studies should be performed to understand the relative contribution of these separate processes to the exposure pattern.

Comment

Measures such as AUC may depend upon the mechanisms cited in the Guidance (release of the drug substance from the drug product and a series of possible presystemic actions), and it also depends upon "systemic" actions on the drug substance after its release from the drug product. In fact, one of the most fundamental physiological factors that affect AUC (for example) is drug clearance. Drug clearance is a systemic action, and it may also be a presystemic action.

C. Bioequivalence

1. IND/NDAs

Paragraph 2, Sentence 1

Inequivalence in IND BE studies may arise because the test product produces higher or lower measures of rate and extent of absorption or because the performance of the test or reference is more variable.

Recommendation

Inequivalence in BE studies may arise because the test product produces higher or lower measures of rate and extent of absorption or because the performance of the test or reference is more variable or because the study has insufficient power to demonstrate existing bioequivalence.

Comment

The fact that inequivalence in BE studies may arise because the study has insufficient power to demonstrate existing bioequivalence should be introduced at this point since it is as likely as the other reasons and introduces the first question to be answered when one is presented with inequivalence in a BE study. Namely, is it a difference in the products, or an inadequate study design.

III. METHODS TO DOCUMENT BA AND BE

A. Pharmacokinetic Studies

1. General Considerations

Sentence 2

This approach rests on an understanding that measuring the active moiety and/or ingredient at the true site of action is generally not possible and, furthermore, that some predetermined relationship between safety and efficacy has already been established relative to the concentration of active moiety and/or ingredient and/or its important metabolite or metabolites in the systemic circulation.

Recommendation

This approach rests on an understanding that measuring the active moiety and/or ingredient at the true site of action is generally not possible and, furthermore, that some relationship between safety and efficacy exists relative to the concentration of active moiety and/or ingredient and/or its important metabolite or metabolites in the systemic circulation.

Comment

It is rare for some predetermined relationship between safety and efficacy to have been established relative to the concentration. However, it is a fundamental dogma of clinical pharmacology that the unbound concentration in plasma drives the unbound concentration to the site of action and, therefore, equivalence of concentration represents equivalence of safety and efficacy.

A. Pharmacokinetic Studies

1. General Considerations

Sentences 4 to 6

A typical study is conducted as a crossover study. In this type of study, clearance, volume of distribution, and absorption, as determined by physiological variables (e.g. gastric emptying, motility, pH), are assumed to have less interoccasion variability compared to variability arising from formulation performance. Therefore, differences between the two products due to formulation factors can readily be determined.

Recommendation

A typical study is conducted as a crossover study. In this type of study, clearance, volume of distribution, and absorption, as determined by physiological variables (e.g. gastric emptying, motility, pH), are assumed to have less interoccasion variability than variability arising from formulation performance. Therefore, differences between the two products are ascribed to formulation factors.

Add an acknowledgement that this is not always the case. When clearance and physiological variables (e.g. gastric emptying, motility, pH) that affect absorption have greater interoccasion variability than variability arising from formulation performance the usual approach to establishing bioequivalence is unreliable. Under those circumstances, the statistical limits of a criterion for demonstration of bioequivalence should reflect the large underlying physiological variability that has nothing to do with the formulations being tested.

Comment

The assumptions underlying a bioequivalence study have been stated. It is now well recognized that there are some drug substances that exhibit large interoccasion variability. Product made from these drug substances cannot be shown to be bioequivalent to themselves via the usual crossover study. For such drug substances differences between two tested products cannot be ascribed to formulation factors.

A. Pharmacokinetic Studies

4. Replicate Study Designs

Replicate study designs (see section IV) are recommended for all BE studies using pharmacokinetic measurements, with the following exceptions: (1) BE studies of drug products containing drug substances with long half lives (e.g., > 96 hours); (2) BE studies in which a steady-state design is needed; and (3) BE studies in which excessive blood collection and/or other safety factors would arise as a result of treatment replication. For BE studies conducted during the IND period, the recommendation applies only to BE studies between the to-be-marketed dose form and pivotal clinical trial batch material. Additional justification for the use of nonreplicate study designs can be provided by sponsors and/or applicants.

Recommendation

This section should be deleted.

Comment

No reason is given for this requirement that essentially all bioequivalence studies should be conducted as replicate designs. One must infer that it is to provide for the implementation of individual bioequivalence (IBE). IBE is not a method accepted by the community of scientists as a valid method of determining the bioequivalence of two products.
A requirement that essentially all bioequivalence studies should be conducted as replicate designs is an onerous burden since such studies are based on a statistical method for bioequivalence that has not been shown to be necessary or statistically robust.

A. Pharmacokinetic Studies

5. Study Population

First Sentence

Unless otherwise indicated by a specific guidance, subjects recruited for in vivo BE studies should be 18 years or older and capable of giving informed consent.

Recommendation

Keep this sentence

Comment

The introduction of eligibility requirements that open up crossover studies to all of the adult population are enthusiastically supported.

A. Pharmacokinetic Studies

5. Study Population

Second Sentence

An attempt should be made to admit as heterogeneous a study population as possible, with a reasonable balance of males and females, young and elderly, and members of differing racial groups.

Recommendation

Delete.

Comment

What is "reasonable?" Is it numbers that represent the proportions of the population in City X of USA that have those demographic characteristics? Is it the same distribution as in the population to be treated with the product? "Reasonable balance" has never been required of bioequivalence studies, and no reason for this requirement has been given. One suspects that an unstated statistical analysis is intended, i.e. an analysis for a group-by-formulation interaction. An important lesson scientists learn and statisticians reinforce is that the objectives of a study should be clear, and the study design and statistical analysis follows the objectives. If a subset analysis or a group-by-formulation analysis is not intended in a bioequivalence study, if it is not a part of the objectives, then it should have no bearing on the determination of bioequivalence. Thus, "a reasonable balance of males and females, young and elderly, and members of differing racial groups", has no place in this Guidance.

A. Pharmacokinetic Studies

8. Pharmacokinetic Measures of Systemic Exposure

a. Early Exposure

Early exposure in a product quality BA study can be assessed by measuring the partial area under the concentration-time profile curve with a cutoff at the peak time (Tmax) of the drug. To establish BE, the partial area is truncated at the time of the peak of the reference formulation in each subject. A minimum of two samples should be collected before the expected peak time to allow adequate estimation of the partial area.

Recommendation

a. Rate of Drug Absorption

Rate of drug absorption in a product quality BA study can be assessed by indirect measures that include the partial area under the concentration-time profile curve with a cutoff at the peak time (Tmax) of the reference drug, Cmax, Tmax, MAT, MRT, and Cmax/AUC. To establish BE, those metrics that can be computed should be reported. A minimum of two samples should be collected before the expected peak time to allow adequate estimation of the selected measures.

Comment

The intent of this PK metric is still to compare products. AUC is well established as a measure of extent of drug bioavailability via the basic pharmacokinetic relationship of the amount of drug gaining access to the sampling medium (blood) and clearance of drug from

that sampling medium. Similarly, a pharmacokinetic understanding of Cmax, Tmax, MAT, MRT, and Cmax/AUC results in an appreciation of the strengths and weaknesses of each to represent the rate at which drug is absorbed. The way in which the proposed new metric (AUC 0-Tmax,ref) relates to the rate at which drug is absorbed, has not been explained. Thus, there is no appreciation of its relative strengths and weaknesses. It is premature to promote this empirical measure to the level of a regulatory metric. The use of a family of metrics, each with known strengths and weaknesses, provides a more complete representation of the relative rate of bioavailability of the products being compared.

D. In Vitro Studies

Under certain circumstances, product quality BA and BE can be documented using in vitro approaches (21 CFR 320.24). For highly soluble, highly permeable, rapidly dissolving, orally administered drug products, documentation of BE using an in vitro approach (dissolution studies) may be appropriate. This approach also may be suitable in some circumstances in assessing BA and BE in the IND period, for NDA and ANDA submissions, and in the presence of certain postapproval changes to approved DAs and ANDAs. In addition, in vitro approaches to document BE for *nonbioproblem* drugs approved prior to 1962 remain acceptable (21 CFR 320.33).

Recommendation

Under certain circumstances, product quality BE can be documented using in vitro approaches (21 CFR 320.24). For highly soluble, highly permeable, rapidly dissolving, orally administered drug products, documentation of BE using an in vitro approach (dissolution studies) may be appropriate. This approach also may be suitable in some circumstances in assessing BE in the IND period, for NDA and ANDA submissions, and in the presence of certain postapproval changes to approved DAs and ANDAs. In addition, in vitro approaches to document BE for *nonbioproblem* drugs approved prior to 1962 remain acceptable (21 CFR 320.33).

Comment

Assessment of BA requires an in vivo study. Prediction of bioavailability based upon in vitro approaches has not been proved. BE (relative BE) can be documented using in vitro approaches. "Product quality BA" is not a sensible term.

IV. COMPARISON OF BA MEASURES IN BE STUDIES

From Sentence 4

More recently, new criteria to allow comparison of BE measurements have been proposed. One, termed an *individual BE criterion*, calls for study designs in which both the test and the reference drug products are administered to the same individuals on two separate occasions (replicate study design). Another, termed a *population BE criterion*, does not involve replicate study design. The recommended individual BE criterion allows assessment of both a subject-by-formulation (S*F) interaction and the within-subject variability of the test and reference products. The recommended population BE criterion allows assessment of total variability of the test and reference products but does not determine the presence or absence of a S*F interaction. Both criteria allow scaling of the BE limit according to the variability of the reference product. Recommended methodologies to allow use of any of three criteria (average, population, individual BE) will be provided in an FDA draft guidance for industry on average, population, and individual approaches to establish equivalence (planned update of a preliminary draft published in December 1997).

This guidance recommends that certain in vivo BE studies conducted for (1) INDs, (2) NDAs, (3) ANDAs, and (4) amendments and supplements to NDAs and ANDAs be conducted using replicate designs (see section III.A.4). Sponsors may analyze their data using either average or population BE criteria (INDs and NDAs) or average or individual BE criteria (ANDAs and supplements to NDAs and ANDAs), provided the choice is specified in the study protocol prior to study initiation. At the sponsor's discretion, scaling may be used to judge BE when either an individual or population BE criterion is specified. Where a replicate fasting study is infeasible, sponsors are encouraged to contact appropriate review staff. In specified circumstances, replicate study designs are not needed (see III.A.4).

Recommendation

Delete this section

Comment

IBE is not a method accepted by the community of scientists as a valid method of determining the bioequivalence of two products. A requirement that essentially all bioequivalence studies should be conducted as replicate designs is an onerous burden since such studies are based on a statistical method for bioequivalence that has not been shown to be necessary or statistically robust. There is an emerging emphasis on the subject-by-formulation interaction as estimated according to the Guidance, "Average, population, and individual approaches to establishing BE". This is a new representation of the old argument that products shown to bioequivalent in healthy young men are not necessarily bioequivalent in patients. There have been many efforts to prove this argument and it has not been accomplished. The broad imposition of replicate design studies and the opinion that $\sigma_D \geq 0.15$ is reason for "concern" has no basis in scientific evidence. Two important elements of scientific evidence are rationality and repeatability. This change to establishing bioequivalence has met neither of these basic scientific criteria.

V. DOCUMENTATION OF BA AND BE

A. Solutions

For oral solutions, elixirs, syrups, tinctures, or other solubilized forms, BE can be established using nonclinical studies (21 CFR 320.22(b)(3)(i)). Solution dosage forms should not contain an inactive ingredient that may significantly affect absorption of the active drug ingredient or active moiety, either in the general population or a subpopulation (21 CFR 320.22 (b) (3) (iii)). Generally, in vivo BE studies are waived for solutions on the assumption that release of the drug substance from the drug product is self-evident and that the solutions do not contain any component that significantly affects drug absorption.

Recommendation

A. Solutions

For oral solutions, elixirs, syrups, tinctures, or other solubilized forms, BE can be established using nonclinical studies (21 CFR 320.22(b)(3)(i)). Solution dosage forms should not contain an inactive ingredient that may significantly affect absorption of the active drug ingredient or active moiety (21 CFR 320.22 (b) (3) (iii)). Generally, in vivo BE studies are waived for solutions on the assumption that release of the drug substance from the drug product is self-evident and that the solutions do not contain any component that significantly affects drug absorption.

Comment

There is no reference to subpopulations in the cited regulation (21 CFR 320.22 (b) (3) (iii)).

C. Immediate-Release Products: Capsules and Tablets

1. General Recommendations

Sentences 4 & 5.

For BE studies for immediate-release dosage forms where the drug product contains a narrow therapeutic range drug (see section VI.F), this guidance recommends the following: (1) where an average BE criterion is selected, use of a BE limit of 90-111 percent for AUC; (2) where an individual BE criterion is selected, reference scaling is recommended, regardless of the variability of the reference listed drug. In addition, this guidance recommends that the allowable upper limit be calculated with $\epsilon_I = 0$ (i.e., $\theta_I = 1.245$).

Recommendation

For BE studies for immediate-release dosage forms where the drug product contains a narrow therapeutic range drug (see section VI.F), this guidance recommends the following: (1) where an average BE criterion is selected, use of a BE limit of 90-111 percent for AUC.

Comment

The application of IBE would be premature. The behavior of this statistic for drug products with low variability has not been well described. Therefore, the application of an individual BE criterion (with reference scaling) is not an appropriate regulatory recommendation.

C. Immediate-Release Products: Capsules and Tablets

2. Exposure Measurements

For orally administered, immediate-release drug products, BE may generally be established by measurements of peak (Cmax) and total exposure (AUC). More rapid or slower release of the active moiety and/or ingredient from a conventional/immediate release dosage form may be important clinically and, in these settings, use of an early exposure measure would be justified. At the request of a sponsor or the reviewing division, application of partial AUC as an early exposure measurement may be justified on the basis of appropriate clinical safety and/or efficacy trials and/or PK/PD studies (see section III.A.8). If the reason for an early exposure measurement can be supported, subsequent BE studies performed by either the pioneer or a generic sponsor, to include BE studies for postapproval change, should use the measurement for comparative analyses. If an early exposure measurement is used, statistical analysis of Cmax is not needed.

Recommendation

For orally administered, immediate-release drug products, BE may generally be established by measurements of extent of exposure/ absorption (AUC) and by rate of absorption (AUC 0-Tmax,ref, Cmax, Tmax, MAT, MRT, and Cmax/AUC).

Comment

The intent of this PK metric is still to compare products. AUC is well established as a measure of extent of drug bioavailability via the basic pharmacokinetic relationship of the amount of drug gaining access to the sampling medium (blood) and clearance of drug from that sampling medium. Similarly, a pharmacokinetic understanding of Cmax, Tmax, MAT, MRT, and Cmax/AUC results in an appreciation of the strengths and weaknesses of each to represent the rate at which drug is absorbed. The way in which the proposed new metric (AUC 0-Tmax,ref) relates to the rate at which drug is absorbed, has not been explained. Thus, there is no appreciation of its relative strengths and weaknesses. It is premature to promote this empirical measure to the level of a regulatory metric. The use of a family of metrics, each with known strengths and weaknesses, provides a more complete representation of the relative rate of bioavailability of the products being compared. The BE limits for evaluation of relative rates of absorption, should take into consideration the family of measures used. The BE limits would be that the mean results for test and reference products be within 20% for at least three out of five metrics.

D. Modified-Release Products

1. NDAs: BA and BE Studies

Second Sentence

For an extended-release Type 3 NDA, if the drug product is not pharmaceutically equivalent and/or bioequivalent to a previously approved drug product (i.e., if pharmaceutically equivalent and bioequivalent), the application should be submitted as an ANDA. BA recommendations for an extended-release NDA product are considered at 21 CFR 320.25(f).

Recommendation

For an extended-release Type 3 NDA, if the drug product is not pharmaceutically inequivalent and/or bioinequivalent to a previously approved drug product (i.e., if pharmaceutically equivalent and bioequivalent), the application should be submitted as an ANDA.

Comment

Check for logical sense.

D. Modified-Release Products

2. ANDAs: BE Studies

Third Sentence

For drugs that exhibit nonlinear kinetics and/or drugs designated as narrow therapeutic range drugs (see section VI.F), this guidance recommends the following: (1) where an average BE criterion is selected, use of a BE limit of 90-111 percent for AUC; (2) where an individual BE criterion is selected, reference scaling is recommended, regardless of the variability of the reference product. In addition, this guidance recommends that the allowable upper limit be calculated with $\epsilon_I = 0$ (i.e., $\theta_I = 1.245$). Where a replicate fasting study is infeasible, sponsors are encouraged to contact appropriate review staff.

Recommendation

For drugs designated as narrow therapeutic range drugs (see section VI.F), this guidance recommends the following: (1) where an average BE criterion is selected, use of a BE limit of 90-111 percent for AUC.

Comment

The application of IBE would be premature. The behavior of this statistic for drug products with low variability has not been well described. Therefore, the application of an individual BE criterion (with reference scaling) is not an appropriate regulatory recommendation. "Drugs that exhibit nonlinear kinetics" is a very broad category. Nonlinearity can reside in various pharmacokinetic processes, including drug release, drug absorption, drug elimination, and drug protein binding. If the real concern is for drugs like phenytoin that exhibit readily detectible nonlinearity of drug elimination in the range of therapeutic concentrations then the Guidance should address this situation.

APPENDIX 2: General Pharmacokinetic Study Design

Study Conduct, Bullet 5

- Prior to and during each study phase, subjects should (1) be allowed water as desired except for one hour before and after drug administration; (2) be provided standard meals no less than 4 hours after drug administration; (3) abstain from alcohol for 48 hours prior to each study period and until after the last sample from each period is collected.

Recommendation

- Prior to and during each study phase, subjects should (1) be allowed water as desired except for one hour before and after drug administration; (2) be provided standard meals no less than 4 hours after drug administration; (3) abstain from alcohol for 12 hours prior to each study dosing.

Comment

The requirement, "abstain from alcohol for 48 hours prior to each study period and until after the last sample from each period is collected", is very extreme considering that an effect of alcohol on drug disposition requires that reasonable amounts be taken while the drug is present in the body. In practical terms, subjects should be supervised throughout the sampling period if one is to be certain that they abstain from alcohol. Supervision throughout the elimination of very long half-lived drugs is not practical. Restrictions of a volunteer subject's activity have to be managed in such a way that the subject is safe and the integrity of the study is also protected. This is best done by designing the study in a manner such that accurate information about a subject's activities can be obtained. Imposition of excessive restrictions on a subject's activities decreases the likelihood of obtaining accurate reports.

Pharmacokinetic information recommended for submission:

- Pharmacokinetic parameter or the metric being calculated
- Plasma concentrations and time points
- Subject, period, sequence, treatment, AUC_{0-t}, $AUC_{0-\infty}$, Cmax, Tmax, and half-life,
- Systemic exposure measurements: Early (Partial AUC), Peak (Cmax), and Total ($AUC_{0-\infty}$)
- Statistical Information on AUC_{0-t}, $AUC_{0-\infty}$, $AUC_{0-t}/AUC_{0-\infty}$, Cmax, Tmax, Kel, half-life, $lnAUC_{0-t}$, $lnAUC_{0-\infty}$, and lnCmax: geometric mean, arithmetic mean, ratio of means, and confidence intervals
- Intersubject, intrasubject, and/or total variability, if available
- Subject-by-formulation interaction variance component ($\int_D^2$), if individual BE criterion is used
- Cmin, Cav, and degree of fluctuation, if steady-state studies are employed. Evidence of attainment of steady state should be provided.

Recommendation

Pharmacokinetic information recommended for submission:

- Plasma concentrations and time points

- Subject, period, sequence, treatment,
- Pharmacokinetic parameters or the metrics: AUC_{0-t}, $AUC_{0-\infty}$, $AUC_{0-t}/AUC_{0-\infty}$, Cmax, Tmax, and half-life, Partial AUC, MAT, MRT, Cmax/AUC, Kel, half-life. Provide individual subject results and descriptive statistics for each treatment.
- Statistical analysis on AUC_{0-t}, $AUC_{0-\infty}$, $lnAUC_{0-t}$, $lnAUC_{0-\infty}$: geometric mean, arithmetic mean, ratio of means, and confidence intervals
- Statistical analysis on Cmax, Partial AUC, MAT, MRT, and Cmax/AUC: Ratio of least squares means.
- Statistical analysis on Tmax: Ratio of nonparametric measure of central tendency.
- Intersubject, intrasubject, and/or total variability, if available
- Cmin, Cav, and degree of fluctuation, if steady-state studies are employed. Evidence of attainment of steady state should be provided.

Comment

Self evident

Rounding off of confidence interval values:

- Confidence interval (CI) values should not be rounded off; therefore, to pass a CI limit of 80-125, the value should be at least 80.00 and not more than 125.00.

Recommendation

Confidence interval (CI) values should be rounded off according to usual conventions. To pass a CI limit of 80-125, the value should be at least 80 and not more than 125.

Comment

The recommendation is unambiguous. The original statement is ambiguous, e.g. for a CI computed to be 79.999 or 125.001. An alternative recommendation would be "Confidence interval (CI) values should be rounded off according to usual conventions to pass a CI limit of 80.00-125.00". Rounding is discussed in GMP Notes.